UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,696	10/28/2005	Shuji Ozaki	14875-141US1 C1-A0220P-US	1270

26161 7590 12/21/2006
FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
GUSSOW, ANNE	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,696	OZAKI ET AL.	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-23 is/are pending in the application.

4a) Of the above claim(s) 1-6 and 13-23 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7-11 is/are rejected.

7)☒ Claim(s) 12 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 28 October 2005 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 11/24/06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group II, Claims 7-12 in the reply filed on November 16, 2006 is acknowledged.

Claims 1-6 and 13-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 16, 2006.

Claims 7-12 are under examination.

Claim Objections

2. Claim 12 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7-11 are indefinite for reciting "increased

activity" in claims 7 and 10 because the exact meaning of the phrase is not clear. Increased activity could be interpreted to mean increased affinity, increased avidity or an increase in a measured downstream step as a result of antibody binding. Also, increased activity compared to what, an antibody not of low molecular weight or to another antibody.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

1. It is unclear if a cell line which produces an antibody having the exact chemical identity of 2D7 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

2. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species 2D7. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

3. It is not clear from the sequence disclosed in the specification as figure 9 encodes the entire sequence necessary to make the 2D7 antibody. Therefore, since it is unclear if the sequence in figure 9 does encode the entire 2D7 antibody, the deposit requirement is necessary.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by DeNardo, et al (Cancer Biotherapy and Radiopharmaceuticals 2001, Vol. 16 No.6, pages 525-535).

The claims recite a method of producing an HLA-recognizing antibody having increased activity by converting an HLA antibody to a low molecular weight diabody.

DeNardo, et al. teach a method of construction of an anti-HLA-DR/anti-DOTA diabody (see figure 1) which can be used to target tumors with ^{90}Y, thus increasing the activity of the antibody. Since the claims do not define the specific increased activity of the diabody, all the limitations of the claims have been met.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 7-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeFelice, et al. (Journal of Immunology 1987, Vol. 139 No. 8, pages 2683-2689) in view of Husdon and Kortt (Journal of Immunological Methods 1999, Vol. 231 pages 177-189).

The claims are drawn to a method for producing an HLA-recognizing antibody having increased activity by converting the antibody to a low-molecular-weight antibody wherein the HLA is a class I HLA-A and the conversion step comprises conversion to a diabody.

DeFelice, et al. teach generation of Fab' and $F(ab')_2$ antibody fragments to HLA-A2 class 1 antigens by digestion with pepsin (page 2684, 1st column, paragraph 5). DeFelice, et al. do not teach the antibody fragments having increased activity or being diabodies. These deficiencies are made up for in the teachings of Hudson and Kortt.

Hudson and Kortt teach single chain Fv antibody fragments with linkers of 3 to 12 residues that form bivalent dimers (diabodies) with increased valency (see page 180 1st column and figures 2 and 3a). Hudson and Kortt also teach that the increased binding valency results in high avidity with increased tumor penetration and fast clearance rates compared to the parent Ig molecule (see page 184 1st column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a diabody comprising the HLA antibody of DeFelice, et al. with the increased valency of Hudson and Kortt.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced the diabody of Hudson and Kortt from the antibody of DeFelice, et al. because Hudson and Kortt teach that there is a significant gain in functional binding affinity in multivalent scFvs (diabodies) over monovalent scFv and Fab fragments (page 184 bottom of 1st column) resulting in multiple binding to two or more target antigens on a single surface (page 184 top of 2nd column). Thus it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of DeFelice, et al. and produce a diabody in view of Hudson and Kortt.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. Claims 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goto, et al (Blood, 1994 Vol. 84 No. 6 pages 1922-1930) as evidenced by the

specification in view of DeNardo, et al. (Cancer Biotherapy and Radiopharmaceuticals, 2002 Vol. 16 No. 6 pages 525-535) and Wu, et al. (Immunotechnology, 1996 Vol. 2 pages 21-36).

The claims have been described supra.

Goto, et al. teach a monoclonal antibody HM1.24 obtained by immunizing mice with human myeloma cells that specifically binds to myeloma and lymphomplasmacytoid cells (page 1926 1st column). As evidenced by the specification the antibody of Goto, et al. is a 2D7 antibody (page 2 lines 1-5 and non-patent literature reference 7). Goto, et al. do not teach a low molecular weight antibody that is a diabody. This deficiency is made up for in the teachings of DeNardo, et al and Adams, et al.

DeNardo, et al. teach a method of construction of an anti-HLA-DR/anti-DOTA diabody (see figure 1).

Wu, et al. teach that diabody molecules have higher tumor uptake and retention in tissues than single chain monomers.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a diabody in the method of DeNardo, et al. using the antibody of Goto, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a diabody in the method of DeNardo, et al. with the antibody of Goto, et al. because DeNardo, et al. teach that the size of radiolabeled antibodies impedes blood clearance and tumor penetration (page

525 last line to top of 526) and that diabodies can be utilized to increase tumor avidity. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success because Wu, et al. teach increased tumor targeting by diabodies was enhanced by the larger size of the diabody leading to increased serum half-life (page 34 1st column). One would reasonably envisage that increased serum half-life would lead to increased activity of a diabody relative to a full-length antibody. Also, DeNardo, et al. teach the diabody which recognizes DOTA can be used to target tumors with DOTA-^{90}Y and this would be "increased activity." Making an antibody that binds 90Y-DOTA would increase the activity. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of Goto, et al. and produce a diabody in the method of DeNardo, et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

December 13, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER